IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Shohei Koide	Art Unit	: 1639
Serial No.	: 09/903,412	Examiner	: Teresa D. Wessendorf
Filed	: July 11, 2001	Docket	: 17027.003US1
Title	: ARTIFICIAL ANTIBODY POLYPEPTIDES		

REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Applicant hereby submits this Reply Brief in response to the Examiner's Answer mailed on May 14, 2008.

If necessary, please charge any required fees or credit overpayment to Deposit Account 50-3503.

(1) Real Party in Interest.

The real party in interest is Research Corporation Technologies, Inc.

(2) Related Appeals and Interferences.

There are no related appeals or interferences.

(3) Status of Claims.

Claims 2, 3, 5, 6 and 9-53 have been canceled. Claims 1, 4, 7, 8 and 54-63 are pending and stand finally rejected. Applicant respectfully appeals the final rejection of claims 1, 4, 7, 8 and 54-63.

(4) Status of Amendments.

No amendments have been have been filed subsequent to the Final Office Action.

(5) Summary of the Claimed Subject Matter.

The claimed subject matter relates to a modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue (claim 1). The claimed subject matter also relates to a modified tenth type III module of fibronectin (FNfn10) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue (claim 57). The claimed subject matter is described throughout the specification, for example, at page 6, lines 19-32; page 18, line 14 through page 20, line 5; page 35, line 4 through page 38, line 30; and at page 63, line 4 through page 77, line 23, and in the Figures referenced to in those sections.

(6) Remaining Ground of Rejection to be Reviewed on Appeal.

The issue being appealed is whether claims 1, 4, 7-8, and 54-63 are patentable under 35 U.S.C. § 103(a) over Koide (WO 98/56915) or Lipovsek *et al.* (U.S. Patent No. 6,818,418) in view of Spector *et al.* (*Biochemistry*, *39*, 872-879 (2000)).

(7) Arguments

Claims 1, 4, 7-8 and 54-63 are patentable over Koide, Lipovsek and/or Spector.

The Examiner rejected claims 1, 4, 7-8 and 54-63 under 35 U.S.C. § 103(a), alleging that those claims are unpatentable over Koide (WO 98/56915; hereinafter Koide) or Lipovsek *et al.* (U.S. Patent No. 6,818,418; hereinafter Lipovsek) in view of Spector *et al.* (*Biochemistry, 39,* 872-879 (2000); hereinafter Spector).

Claims 1 and 57 are independent claims. Independent claim 1 recites a modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue. Claims 4, 7-8 and 54-56 depend directly or indirectly from claim 1. Claim 4 recites the modified, stabilized Fn3 of claim 1, wherein Asp7 or Asp23, or both, have been substituted with an asparagine (Asn) or Lysine (Lys) residue. Claim 7 recites that Glu 9 of the modified, stabilized Fn3 has been substituted with an asparagine (Asn) or lysine (Lys) residue. Claim 8 recites that all three of Asp7, Asp23 and Glu9 o f the modified, stabilized Fn3 have been substituted with at least one other amino acid residue. Claims 54-56 are directed to modified Fn3 molecules that comprise a stabilizing mutation that is a substitution of at least one of Asp7, Asp23 or Glu 9 with a neutral or positively charged amino acid residue (claim 54) or with a neutral amino acid residue (claim 55) or with a positively charged amino acid residue (claim 56).

The second independent claim, claim 57, recites a modified tenth type III module of fibronectin (FNfn10) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue. Claims 58-63 depend directly or indirectly from claim 57. Claims 58-60 are directed to modified FNfn10 molecules that comprise a stabilizing mutation that is a substitution of at least one of amino acid residues 7, 9 or 23 with a neutral or positively charged amino acid residue (claim 58) or with a neutral amino acid residue (claim 59) or with a positively charged amino acid residue (claim 60). Claims 61-63 are directed to the modified, stabilized FNfn10 of claim 57, wherein Asp 7 or Asp 23, or both, have been substituted with an asparagine (Asn) or lysine (Lys) residue. Claim 61 recites that amino acid residues 7 or 23, or both, of the modified, stabilized FNfn10 has been substituted with an asparagine (Asn) or lysine (Lys)

residue. Claim 62 recites that amino acid residue 9 has been substituted with an asparagine (Asn) or lysine (Lys) residue. Claim 63 recites that all three of Asp7, Asp 23 and Glu9 of the modified, stabilized FNfn10 have been substituted with at least one other amino acid residue.

The Supreme Court has set out the analysis for patentability under 35 USC 103(a): the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined (*see, e.g., Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007)). Further, the cited documents must be considered in their entirety, and it is not permissible to pick and choose from any one document only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such document fairly suggests to one of ordinary skill in the art (*see, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986) and *In re Wesslau*, 353 F.2d 238, U.S.P.Q. 391 (C.C.P.A. 1965)). Applicants submit that the level of ordinary skill in the pertinent art is high. The scope and content of the prior art and the differences between the prior art and the claims at issue are discussed herein below, as are the reasons the claims are not obvious in view of the cited documents.

Applicant respectfully submits that the Examiner has not demonstrated that the claims are obvious in view of the cited documents, for example, because the Examiner has not established that the cited documents teach or suggest all the claim limitations. And, even if, for the sake or argument, the cited documents teach or suggests all the claim limitations, Applicant respectfully submits that the Examiner has not established the suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention. Further, Applicant respectfully submits that the Examiner is improperly relying on an "obvious to try" rationale.

Koide relates to Fn3 polypeptide monobodies. Koide teaches that "though the introduced mutations in the two loops certainly decreased the stability of Ubi4-K relative to wild-type Fn3, the stability of Ubi4 remains comparable to that of a "typical" globular protein" (page 53, lines 14-18), and that the "Ubi4-K protein retained the global fold of Fn3, showing that this scaffold can accommodate a large number of mutations in the two loops tested. Though the stability of

the Ubi4-K protein is significantly lower than that of the wild-type Fn3 protein, the Ubi4 protein still has a conformational stability comparable to those for small globular proteins" (page 53, lines 26-30). It should be noted that only mutant fibronectin molecules with reduced stability relative to wild type fibronectin are disclosed in Koide (*e.g.*, Figure 16 and Example XVII). Thus, Koide teaches that the wild-type Fn3 is such a stable molecule, that modifications can be introduced into the wild-type molecule that will reduce the stability of the molecule, and it will still be stable as compared to other small globular proteins. Koide does not teach the introduction of a stabilizing mutation into an Fn3 molecule as recited by the pending claims. Nor does Koide teach the substitution of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3. Further, Koide does not teach or suggest that residues 7, 9 or 23 of Fn3 are involved in unfavorable electrostatic interactions.

Lipovsek relates to antibody mimics that are based on the structure of an Fn3 (column 7, lines 63-65). Lipovsek states that for the human ^{10}Fn3 sequence, at a minimum, amino acids 1-9, 44-50, 61-54, 82-94 (edges of beta sheets); 19, 21, 30-46 (even), 79-65 (odd) (solvent-accessible faces of both beta sheets); 21-31, 51-56, 76-88 (CDR-like solvent-accessible loops); and 14-16 and 36-45 (other solvent-accessible loops and beta turns) may be randomized to evolve new or improved compound-binding proteins (column 9, lines 24-31). Thus, Lipovsek indicates that one might consider modifying any of about 80 of the 95 amino acids in the Fn3 molecule to generate a protein with improved compound-binding capabilities. This, however, does not provide a finite number of identified, predictable solutions, with a reasonable expectation of success. Further, Lipovsek is suggesting the modification of the residue for an entirely different purpose. Applicant submits that a need to try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, is an improper application of the "obvious to try" rationale (*see* M.P.E.P. § 2145(X)(B)). Further, Lipovsek doest not teach the introduction of a stabilizing mutation into the Fn3 molecules. Nor does Lipovsek teach the substitution of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3. Moreover, Lipovsek does not teach or suggest that residues 7, 9 or 23 are involved in unfavorable electrostatic interactions.

The Examiner acknowledges that neither Koide nor Lipovsek teaches that the regions of Fn3 containing amino acids 7, 9 and 23 are involved in an unfavorable electrostatic interaction. Applicant respectfully submits that Spector does not remedy the deficiencies of Koide and Lipovsek. Spector relates to the electrostatic contributions that charged and polar side chains make on the overall stability of a 41-residue peripheral subunit-binding domain protein derived from the dihydrolipoamide acetyltransferase component of the pyruvate dehydrogenase multienzyme complex from *Bacillus stearothermophilus* (page 873, first column, second full paragraph). It should be noted that this *B. stearothermophilus* protein discussed by Spector is a different protein than the Fn3 protein recited in the claims.

Spector does not teach or suggest that the regions of Fn3 containing amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction. Applicant submits that the Examiner has not established that the cited documents teach or suggest all the claim limitations, *e.g.*, a modified Fn3 or FNfn10 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3 or FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 (*e.g.*, Asp 7, Asp 23 or Glu 9) with another amino acid residue. None of the references teach which amino acid residues in an Fn3 molecule are involved in an unfavorable electrostatic interaction, and therefore, might be desirable to mutate in order to remove an unfavorable electrostatic interaction as compared to the wild-type Fn3.

It should further be noted that even in the passages from Spector cited by the Examiner, there was significant uncertainty regarding whether the residues in their *B. stearothermophilus* protein that they thought were involved in an unfavorable electrostatic interaction were indeed unfavorably involved, and if replace would improve the protein's stability. They indicated that in their protein, the Arg8 may interact unfavorably, and that theirs is another arginine on the same face of the helix at position 12, four residues away form Arg8, and these two residues could also interact unfavorably, and that replacement of Arg8 with a hydrophobic residues should eliminate these unfavorable electrostatic interactions (p. 875). Further, regarding the possible applicability to other molecules that would inherently have different conformations, uncertainty is evident by Spector's comments on page 879 that states that their results suggest that optimization of surface electrostatic interactions is likely to be a generally applicable strategy for enhancing protein stability; they were not certain that it would be true. Further, at

page 878, column 1, first paragraph of the Discussion, Spector states that the while substitution of Arg8 resulted in a significant increase in stability, that increase was much smaller than predicted. Thus, Applicant submits that the cited documents do not teach or suggest that the specific amino acid residues of Asp 7, Asp 23 or Glu 9 of Fn3 are involved in an unfavorable electrostatic interaction, much less that those amino acids could be substitute in order to generate an Fn3 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3. Accordingly, when considered in their entirety, the combination of the cited documents does not yield a predictable result.

The Examiner states at page 8 of the Examiner's Answer that "appellant cannot attack the references individually when the rejection is based on the combination of the references." However, the cited documents must be considered in their entirety, and it is not permissible to pick and choose from any one document only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such document fairly suggests to one of ordinary skill in the art (*see, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q. 416 (Fed. Cir. 1986) and *In re Wesslau*, 353 F.2d 238, U.S.P.Q. 391 (C.C.P.A. 1965)). Applicant respectfully submits that, when considered in their entirety, the claims are not obvious in view of any of the cited documents.

Thus, Applicant respectfully submits that the cited documents, neither alone nor in combination, teach all of the elements recited in the present claims. The combination of cited documents do not teach or suggest a modified Fn3 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue. Nor do the cited documents, either alone or in combination, teach a FNfn10 molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue. Further, Applicant submits that the Examiner has not established the suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine

document teachings so as to arrive at the claimed invention. Thus, Applicant respectfully requests that the Board withdraw the rejection of the claims under 35 U.S.C. § 103(a).

Each claim is argued separately.

Applicant respectfully submits that the Examiner has not separately demonstrated that any of claims 1, 4, 7-8 or 54-63 are separately *prima facie* obvious in view of the cited documents, for example, because the Examiner has not established that the cited documents teach or suggest the claim limitation of each separate claim. And, even if, for the sake or argument, the cited documents teach or suggests all the claim limitations, Applicant respectfully submits that the Examiner has not established the suggestion or motivation, either in the cited documents themselves or in the knowledge generally available to an art worker, to modify the documents or to combine document teachings so as to arrive at the claimed invention of each separate claim. Because of the specific elements of each claim, each claim is argued separately.

1. Claim 1

As described hereinabove, Applicant respectfully submits that claim 1, which is directed to modified Fn3 molecules comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue, is patentable over Koide, Lipovsek and/or Spector.

2. Claim 4

Claim 4 depends from claim 1 and specifically recites that for the modified Fn3 molecule, Asp 7 or Asp 23, or both, have been substituted with an asparagine (Asn) or lysine (Lys) residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified Fn3 molecule.

3. Claim 7

Claim 7 depends from claim 1 and specifically recites that for the modified Fn3 molecule, Glu 9 has been substituted with an asparagine (Asn) or lysine (Lys) residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector

teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified Fn3 molecule.

4. Claim 8

Claim 8 depends from claim 1 and specifically recites that for the modified Fn3 molecule, Asp 7, Asp 23, and Glu 9 have been substituted with at least one other amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified Fn3 molecule.

5. Claim 54

Claim 54 depends from claim 1 and specifically recites that for the modified Fn3 molecule, the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a neutral or positively charged amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified Fn3 molecule.

6. Claim 55

Claim 55 depends from claim 54 and specifically recites that for the modified Fn3 molecule, the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a neutral amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified Fn3 molecule.

7. Claim 56

Claim 56 depends from claim 54 and specifically recites that for the modified Fn3 molecule, the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a positively charged amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified Fn3 molecule.

8. Claim 57

As described hereinabove, Applicant respectfully submits that claim 57, which is directed to modified FNfn10 molecules comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue, is patentable over Koide, Lipovsek and/or Spector.

9. Claim 58

Claim 58 depends from claim 57 and specifically recites that for the modified FNfn10 molecule, the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with a neutral or positively charged amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified FNfn10 molecule.

10. Claim 59

Claim 59 depends from claim 58 and specifically recites that for the modified FNfn10 molecule, the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with a neutral amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified FNfn10 molecule.

11. Claim 60

Claim 60 depends from claim 58 and specifically recites that for the modified FNfn10 molecule, the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with a positively charged amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified FNfn10 molecule.

12. Claim 61

Claim 61 depends from claim 58 and specifically recites that for the modified FNfn10 molecule, amino acid residues 7 or 23, or both, have been substituted with an asparagine (Asn) or lysine (Lys) residue. Applicant submits that the Examiner has not demonstrated that any of

Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified FNfn10 molecule.

13. Claim 62

Claim 62 depends from claim 58 and specifically recites that for the modified FNfn10 molecule, amino acid residue 9 has been substituted with an asparagine (Asn) or lysine (Lys) residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified FNfn10 molecule.

14. Claim 63

Claim 63 depends from claim 57 and specifically recites that for the modified FNfn10 molecule, amino acid residues 7, 9 and 23 have been substituted with at least one other amino acid residue. Applicant submits that the Examiner has not demonstrated that any of Koide, Lipovsek and/or Spector teach such an element, nor has the Examiner established the suggestion or motivation to modify the documents or to combine document teachings so as to arrive such a modified FNfn10 molecule.

At page 2 of the Final Office Action, the Examiner objected to a hyperlink in the specification. Applicant will amend the objected-to paragraph to correct the hyperlink upon notification of allowable claims.

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is respectfully requested. If necessary, please charge any required fees or credit overpayment to Deposit Account 50-3503.

Respectfully submitted,
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(8) Claims Appendix.

1. A modified fibronectin type III (Fn3) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type Fn3, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with another amino acid residue.

4. The Fn3 of claim 1, wherein Asp 7 or Asp 23, or both, have been substituted with an asparagine (Asn) or lysine (Lys) residue.

7. The Fn3 of claim 1, wherein Glu 9 has been substituted with an asparagine (Asn) or lysine (Lys) residue.

8. The Fn3 of claim 1, wherein Asp 7, Asp 23, and Glu 9 have been substituted with at least one other amino acid residue.

54. The Fn3 of claim 1, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a neutral or positively charged amino acid residue.

55. The Fn3 of claim 54, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a neutral amino acid residue.

56. The Fn3 of claim 54, wherein the stabilizing mutation is a substitution of at least one of Asp 7, Asp 23 or Glu 9 with a positively charged amino acid residue.

57. A modified tenth type III module of fibronectin (FNfn10) molecule comprising a stabilizing mutation of at least one residue involved in an unfavorable electrostatic interaction as compared to a wild-type FNfn10 molecule, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with another amino acid residue.

58. The modified FNfn10 of claim 57, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with a neutral or positively charged amino acid residue.

59. The modified FNfn10 of claim 58, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with a neutral amino acid residue.

60. The modified FNfn10 of claim 58, wherein the stabilizing mutation is a substitution of at least one of amino acid residues 7, 9 or 23 with a positively charged amino acid residue.

61. The modified FNfn10 of claim 58, wherein amino acid residues 7 or 23, or both, have been substituted with an asparagine (Asn) or lysine (Lys) residue.

62. The modified FNfn10 of claim 58, wherein amino acid residue 9 has been substituted with an asparagine (Asn) or lysine (Lys) residue.

63. The modified FNfn10 of claim 57, wherein amino acid residues 7, 9 and 23 have been substituted with at least one other amino acid residue.

(9) Evidence Appendix.

A. WO 98/56915

Please refer to the Information Disclosure Statement mailed on April 11, 2002.

B. U.S. Patent No. 6,818,418

Please refer to the Information Disclosure Statement mailed on July 11, 2001.

C. Spector *et al.* "Rational modification of protein stability by the mutation of charged surface residues", *Biochemistry*, *39*, 872-879 (2000).

Please refer to the Information Disclosure Statement mailed on September 21, 2005.

(10) Related Proceedings Appendix.

There have been no decisions rendered by a court or the Board in the appeal of Application Serial No. 09/903,412.